Hepatocellular Carcinoma Column

The expression level of Myeloid differentiation factor 88 might be a significant biomarker for the prognosis of HCC patients

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Dr. Liang *et al*. reported that myeloid differentiation factor 88 (MyD88) could promote the growth and metastasis of human hepatocellular carcinoma (HCC) using clinical human HCC samples, *in vitro* analysis and an *in vivo* mouse model (1). It has been reported that MyD88 could interact with TIR domain of Toll/IL-1 receptor as a TIR-domain-containing adaptor protein. MyD88 recruits interleuikin-1 receptor-associated kinase and tumor necrosis factor receptor associated factor-6, leading to the activation of NF-κB and mitogen-activated protein kinases (MAPKs). Recently, many groups have reported that immune cells could contribute to inflammation-associated carcinogensis in the tumor microenvironment. MyD88 was found to be critical for the production of IL-6 in Kupffer cells. In addition to Kupffer cells, myeloid derived suppressor cells (MDSCs) could contribute to the tumor progression by suppressing effector immune cells. MDSCs obtained from tumor-bearing MyD88(–/–) mice failed to suppress the antigen-specific proliferation of $CD8^+$ T cells and $CD4^+$ T cells, whereas MDSCs from wild-type mice significantly suppressed both types of T cells (2). Moreover, it has been reported that the increase in the frequency of MDSCs was mediated by MyD88-NF-kB pathway (3). Interestingly, tumor-derived exosomes-associated HSP72 could trigger STAT-3 activation in MDSCs in a TLR2/MyD88–dependent manner through the autocrine production of IL-6 (4). These data might influence the results concerning the relationship between the MyD88 expression levels and inflammation. On average, similar amounts of CD68+ cells were found intra-tumor or peri-tumor with no significant difference between HCC tissues with high or low MyD88 expression. MyD88 could contribute to the activation of Kupffer cells in addition to MDSCs that are important subsets for immune suppression. The complexity of immune activation and suppression could not be explained by MyD88 expression in Dr. Liang's study. In addition to immune reactions, several findings showed MyD88 could act intrinsically to promote carcinogenesis by noninflammatory functions. However, little is known about the expression of MyD88 in human HCCs and its correlation with tumor development. Thus, Dr. Liang *et al*. analyzed the MyD88 in 110 cases of HCCs and evaluated its correlation with the clinicopathologic characteristics. Moreover, the effects of hepatic MyD88 on cell survival, proliferation and invasion were assessed *in vitro* and *in vivo*.

They showed that MyD88 was frequently up-regulated in HCCs, and was closely related to a worse stage of tumor and higher recurrent rate in HCC patients. Kaplan-Meier analysis showed that recurrence-free survival (P=0.011) and overall survival (P=0.022) were significantly worse in patients with high MyD88-staining. Moreover, the statistical analysis showed that MyD88 expression was not significantly correlated with age, gender, HBsAg, serum AFP level, cirrhosis, vascular invasion or tumor number. However, the evaluation of immunostaining might sometimes be subjective. In Dr. Liang's study, immunostaining of MyD88 was evaluated by two experienced pathologists with a detailed scoring system. Although the results of immunostaining in their study were reliable, a prospective and sequential study should be performed to determine the importance of MyD88 expression.

In terms of functional aspect of MyD88, the knock down of MyD88 greatly inhibited cell proliferation and increased apoptotic cells under the stimulation of serum starvation. Moreover, it has been found that the

overexpression of MyD88 promoted invasion and metastasis in HCC. Moreover, the overexpression of MyD88 could promote the activation of NF-κB, PI3K/AKT, and p38/ERK in HCC cells. NF-κB is one of the main downstream signaling components of TLR/MyD88 signaling, and it is constitutively activated in HCC. They also found that NF-κB activation could occur via a TLR/IL-1R signaling-independent manner. These results very clearly demonstrated that an elevation of MyD88 in hepatocytes is involved in the tumor progression and may serve as a prognostic factor for HCC patients. Interestingly, another group reported that HBx could stimulate IL-6 expression in hepatocytes via a MyD88-dependent-manner. HBx promotes cancer stem cells with EpCAM by activating β-catenin and epigenetic up-regulation of miR181. In addition, Chisari and Ferrari reported that HBx protein generates cancer stem cells from hepatic progenitor cells. We think that the likelihood of HBx acting as a promoting factor for cancer stem cells is high, but that this would not explain everything. Recently, we also reported that the expression of EpCAM increases in hepatitis B virus (HBV) related HCC using clinical samples (5). HBV is known to develop HCC faster than other etiologies. Carcinogenesis from HBV appeared at ages about ten years younger than that from other etiologies in this study. Although several mechanisms have been suggested to explain the formation of HCC in chronic hepatitis B patients, the mechanism still remains uncertain. The expression of MyD88 might contribute to the carcinogenesis and prognosis of HBV-related HCC. In Dr. Liang's report, most of the patients were HBsAg positive. Therefore, a relationship between MyD88 expression and HBV infection could not be detected in their study. We should consider whether another etiology might influence the importance of MyD88 expression.

Not only it is important to understand the refractory clinical pathogenesis of HCC, but their discovery is also very useful in providing a prognostic value in HCC.

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